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10/524,609	02/14/2005	Gabriels E. Joseph Jr.	MCA-614 US	9978

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MILLIPORE CORPORATION
290 CONCORD ROAD
BILLERICA, MA 01821

EXAMINER
LIU, SUE XU

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,609	JOSEPH JR. ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date ____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 4-15 have been cancelled as filed on 6/7/07.

Claims 1-3 and 16-20 are currently pending.

Claims 1-3 and 16-20 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of Group 1 (Claims 1-3 and 16-20) in the reply filed on 6/7/07 is as previously acknowledged.

Priority

3. This application is filed under 35 U.S.C 371 of PCT/US03/26557 (filed on 08/25/2003), which claims priority to US provisional applications 60/406,654 (filed on 8/28/2002).

Claim Objection(s) / Rejection(s) Withdrawn

4. In light of applicants' amendments to the claims to clarify the claim language, the following claim rejection as set forth in the previous office action is withdrawn:

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Objection(s) / Rejection(s) Maintained

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Note: the instant claim numbers are in bold font.)

Leonard and Bjerke

6. Claims 1-3 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leonard et al (WO 01/19482; 3/22/2001; cited in IDS), in view of Bjerke et al (WO 02/44414; 6/6/2002; priority date 11/21/2001 or earlier; cited in IDS). The previous rejection is maintained for the reasons of record as set forth in the Office action as well as the reasons below.

The instant claims recite a method for purifying sequencing reaction product by removing unincorporated dye terminators from a sequencing reaction, comprising: providing sequencing reaction product; providing at least one ultrafiltration membrane having at least one surface; providing a solution comprising an amount of guanidine effective for removing unincorporated dye terminators from said sequencing reaction; introducing said sequencing reaction product and said solution to said at least one surface of said ultrafiltration membrane; applying a driving force to said ultrafiltration membrane to produce purified sequencing reaction product by removing unincorporated dye terminators from the sequencing reaction product.

Leonard et al, throughout the publication, teach a method of purifying sequencing reaction product using ultrafiltration membrane to remove contaminant such as unincorporated dye terminators (e.g. Abstract; p.2, lines 5+, lines 24+), which read on the removing of unincorporated dye terminators of **clm 1**. The reference teaches providing a quantity of sequencing reaction product and one ultrafiltration membrane (e.g. Claim 1 of the reference), which reads on the first two steps of **clm 1**. The reference also teaches suspending the sequencing reaction products in a solvent such as formamide solution and applying the mixture to the membrane (e.g. p.5, para 2; Claims 1, 4 and 5), which read on the steps of providing a solution and introducing the mixture to the membrane of **clm 1**. The reference also teaches applying a force or a pressure to the membrane (e.g. Claims 1 and 6), which read on the last step of **clm 1**. The reference also teaches resuspending the sequencing product in various solvents such as water (e.g. Claim 23), which reads on the low ionic solution of **clm 2**. The reference also teaches subsequent electrophoresis for DNA separation (a part of sequencing step) (e.g. p.2, line 9+; p.6, lines 6+) and/or mass spectroscopy (e.g. p.6, lines 6+), which read on the step of **clm 3**.

Leonard et al do not explicitly teach using a guanidine containing solution for the purification solution as recited in **clms 1** (step 3) and **clms 17**.

However, Bjerke et al, throughout the publication, teach purification of DNA sequencing products using magnetic particles and chaotropic agent such as guanidine solutions (e.g. Abstract; p.3, lines 1+; p. 6, lines 30+). The reference teaches dissolving the DNA sequencing product in the chaotropic guanidine solution (e.g. pp.17+), which reads on the solution comprising dye terminators of **clm 17** because the sequencing product comprises dye terminators. The Bjerke reference also teaches the advantages of using a "chaotropic agent"

(such as guanidine solution) including making denatured nucleic acids thermodynamically more stable than their correctly folded or structured counterparts (p.6, lines 23+).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to add a chaotropic agent such as a guanidine solution for the purification of DNA.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a chaotropic agent such as guanidine for purification of DNA such as sequencing reaction products, because chaotropic agents such as guanidine were known in the art for DNA purification and chaotropic agents were known to enhance nucleic acid binding to solid support for purification, as taught by Bjerke et al (e.g. p.3, lines 1+; p.13, lines 1+). In addition, Bjerke et al also teach the advantages of using a "chaotropic agent" (such as guanidine solution) including making nucleic acids thermodynamically more stable than their correctly folded or structured counterparts when denatured (p.6, lines 23+), and thus one of ordinary skill in the art would have been motivated to include a "chaotropic agent" (such as guanidine) to stabilize denatured nucleic acids such as under the DNA purifying conditions (using formamide) as taught by Leonard or single stranded DNA (such as it is required for DNA sequencing). Thus, it would have been obvious to a person of ordinary skill in the art to try to include a chaotropic agent such as guanidine in an attempt to provide an improved method of purifying sequencing products (i.e. DNA products), as a person with ordinary skill has good reason to pursue the known options within his or her technical grasp. In addition, because both of the Leonard and the Bjerke references teach using various denaturing (or denatured DNA stabilizing agents) in processing DNA (dissolving DNA sequencing product for further purification and/or processing), it would

have been obvious to one skilled in the art to substitute one type of DNA stabilizing solution (e.g. formamide solution) for the other (e.g. guanidine solution) to achieve the predictable result of dissolving DNA sequencing product for further purification and/or processing.

A person of ordinary skill in the art would have a reasonable expectation of success of achieving such modifications since the techniques for using various substrates (such as membranes) for purification of DNA using chaotropic agents such as guanidine solutions are routine and known in the art as demonstrated by Leonard et al and Bjerke et al.

Discussion and Answer to Argument

7. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection by attaching each of the cited combination of references alone. (Reply, pp.6+). Applicants further states "there must be some objective teaching, suggestion or motivation in the prior art..." (Reply, p.7).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, applicants are also respectfully directed to the recent Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.*

Applicants argue the Leonard reference "fails to teach, hint or even suggest using guanidine to remove unincorporated dye terminators... on a filtration membrane..." (emphasis in original; Reply, pp.6+).

The above said rejection is over the combination of the Lenoard and Bjerke references, but not just over the Leonard reference alone. Applicants are respectfully directed to the above rejection for discussion on how the combination of the said references renders the instant claimed invention obvious.

Applicants also argue the Bjerke reference fails to "cure the deficiencies of Leonard". Applicants also assert because the Bjerke reference teaches using the "guanidine" with "silica magnetic particles", the reference "fails to teach, hint or even suggest using guanidine without the silica magnetic particles." (Reply, p.7).

Contrary to applicants' assertion, the combination using silica magnetic particles and guanidine for processing DNA is only one embodiment of the reference's teaching.

Applicants are respectfully directed to MPEP 2123: "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

As discussed supra, the Bjerke reference teaches using "chaotropic agents" in general for processing DNA. In particular, the Bjerke reference teaches the following:

"The term "chaotropic agent" as used herein refers to salts of particular ions which, when present in a sufficiently high concentration in an aqueous solution, cause proteins present therein

to unfold and nucleic acids to lose secondary structure. It is thought that chaotropic ions have these effects because they disrupt hydrogen-bonding networks that exist in liquid water and thereby make denatured proteins and nucleic acids thermodynamically more stable than their correctly folded or structured counterparts. Chaotropic ions include guanidinium, iodide, perchlorate, and trichloroacetate. Chaotropic agents include guanidine hydrochloride, guanidine thiocyanate (which is sometimes referred to as guanidine isothiocyanate), sodium iodide, sodium perchlorate, and sodium trichloroacetate."

(spec. p.6, lines 23+).

Thus, one of ordinary skill in the art would have been motivated to include a "chaotropic agent" (such as guanidine) to stabilize denatured nucleic acids as it is the case when purifying DNA sequencing products.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a chaotropic agent such as guanidine for purification of DNA such as sequencing reaction products, because chaotropic agents such as guanidine were known in the art for DNA purification and chaotropic agents were known to enhance nucleic acid binding to solid support for purification, as taught by Bjerke et al (e.g. p.3, lines 1+; p.13, lines 1+). In addition, Bjerke et al also teach the advantages of using a "chaotropic agent" (such as guanidine solution) including making nucleic acids thermodynamically more stable than their correctly folded or structured counterparts when denatured as well as denaturing proteins (p.6, lines 23+) (such as the ones involved in DNA sequencing reaction) to enhance DNA purification process, and thus one of ordinary skill in the art would have been motivated to include a "chaotropic agent" (such as guanidine) to stabilize denatured nucleic acids such as under the DNA purifying conditions as taught by Leonard. Thus, it would have been obvious to a person of ordinary skill in the art to try to include a chaotropic agent such as guanidine in an attempt to provide an improved method of purifying sequencing products (i.e. DNA products), as a person with ordinary skill has good reason to pursue the known options within his or her technical grasp. In addition, because both of

the Leonard and the Bjerke references teach using various denaturing (or denatured DNA stabilizing agents) in processing DNA (dissolving DNA sequencing product for further purification and/or processing), it would have been obvious to one skilled in the art to substitute one type of DNA stabilizing solution (e.g. formamide solution) for the other (e.g. guanidine solution) to achieve the predictable result of dissolving DNA sequencing product for further purification and/or processing.

In addition, the Bjerke reference does NOT teach that the "chaotropic agent" such as guanidine salts can only be used with "silica magnetic particles". In other words, the Bjerke reference does not teach the DNA (denatured) stabilizing property of guanidine salts can only be realized in the presence of "silica magnetic particles". In fact, the DNA (denatured) stabilizing property of the chaotropic agents such as guanidine salts is an inherent property of the said agents as evidenced by Bjerke et al. Further, the Bjerke reference does not teach guanidine salts can not be used with any other solid substrates for the purpose of DNA purification using an ultrafiltration membrane while applying a driving force.

Leonard and Others

8. Claims 1-3 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leonard et al (WO 01/19482; 3/22/2001; cited in IDS), in view of Bjerke et al (WO 02/44414; 6/6/2002; priority date 11/21/2001 or earlier; cited in IDS), and further in view of Brody et al (US 5,958,727; 9/28/1999) and Rando (US 5,202,456; 4/13/1993).

Leonard et al, throughout the publication, teach a method of purifying sequencing reaction product using ultrafiltration membrane to remove contaminant such as the dye terminators, as discussed above.

Bjerke et al, throughout the publication, teach purification of DNA sequencing products using magnetic particles and chaotropic agent such as guanidine solutions, as discussed above.

The combination of Leonard et al and Bjerke et al references does not explicitly teach using 1mM to 60mM guanidine solution as recited in clms 18-20. The combination of said references also does not explicitly teach the solution comprises EDTA as recited in clm 16.

However, Brody et al, throughout the patent, teach using various reagents and buffers for purification of various polynucleotides (e.g. Abstract). The reference teaches using solutions comprising 50mM Guanidine and EDTA for purification of DNA (e.g. col. 38, lines 63+), which the guanidine concentration falls within the concentration ranges of clms 18 and 19, as well as EDTA of clm 16.

Rando, throughout the patent, teaches using a guanidine solution with a concentration of 7mM for biological applications (e.g. col.7, line 54), which the concentration falls within the range recited in c**lm 20**.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to using guanidine solutions with various concentrations as well as including EDTA in the solution.

A person of ordinary skill in the art would have been motivated at the time of the invention to use guanidine solution with various concentrations depending on the experimental design and the desired applications, as taught by Bjerke et al, Brody et al, and Rando. In

addition, it would have been obvious to one skilled in the art to substitute one concentration for another as the various concentrations are known and routinely used in the art for manipulation of biological molecules such as DNA to achieve the predictable result of binding DNA to a substrate and subsequent purification of the DNA.

A person of ordinary skill in the art would have been motivated at the time of the invention to include EDTA in the solution, because EDTA is known and routinely used in the art for DNA manipulation such as the buffers taught by Brody et al. One skilled in the art would add EDTA as part of a solution to achieve the predictable result of DNA purification.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since the techniques for using various concentrated guanidine solutions and solutions with EDTA for biological reactions such as DNA purification are routine and known in the art as demonstrated by Bjerke et al, Brody et al, and Rando.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with the same argument as the traversal over the combination of the Leonard and Bjerke references. Thus, applicants are respectfully directed to the discussion under the Leonard and Bjerke references for answer to arguments.

Conclusion

THIS **ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Examiner, Art Unit 1639
6/2/08

/Jon D. Epperson/
Primary Examiner, AU 1639